

PUBLIC HEALTH/WORKER SAFETY

Title: Assessment of alternatives for monitoring antimicrobial use in the swine industry and design and implementation of a pilot system (#15-186)

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Industry Summary:

Societal concerns about antibiotic use (ABU) and antibiotic resistance are a major vulnerability for the US swine industry. National and international events have led to increasing pressures for accountability regarding ABU in food animals. These include calls for better measurement of ABU in all sectors (including human medicine and food animal production) and for more responsibility and accountability for antibiotic use by all parties involved in provision and administration of antibiotics.

This project was undertaken to help the US swine industry to remain at the forefront on this issue, and focused specifically on measurement of antibiotic use. The objectives were to 1) Research and identify metrics of value to the pork industry for continual improvement of antibiotic use practices; 2) Assess sources of data and record keeping systems to support ABU measurement; and 3) Develop a framework to protect confidentiality of cooperating producers that provide data on ABU. Projected outcomes of the project were 1) A white paper providing a detailed assessment of options for measuring ABU in the US swine industry; 2) Design of a pilot program based on the white paper; and 3) Initial implementation of the pilot study of ABU.

The white paper was submitted to NPB as part of an interim report in April 2016, just after the FDA had issued a Funding Opportunity Announcement directed at measurement of ABU in major food animal species. The NPB and NPPC encouraged the PI to submit a proposal to that FDA call, which was submitted in May 2016. The FDA proposal, a combined proposal for the avian and swine industries (PI. Dr. Randall Singer, Co-PI. Dr. Peter Davies) was funded by FDA commencing in September 2016 with a projected 5 year duration (2016 – 2021). From that time, the FDA funded project has driven the ongoing evolution of the work initiated in project #15-186. However, this represents an expansion of the original scope of #15-186 rather than a fundamental change in direction. The goals specified in the FDA call were:

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- *Provide detailed antimicrobial drug use data that accurately reflects actual on-farm use;*
- *Provide “baseline” data on antimicrobial use (i.e., data prior to the implementation of Guidance For Industry (GFI) #213*
- *Pilot methodologies for collecting, summarizing, and reporting antimicrobial use data;*
- *Foster public-private partnerships/collaboration;*
- *Leverage existing data systems and minimize burden and disruption to animal producers;*
- *Incorporate strategies for protecting farm/producer identity and other confidential information.*

The April 2016 white paper included several recommendations to advance the overall effort including:

- Formation of a technical committee on ABU surveillance to direct industry leadership on ABU initiatives. Priority issues identified for the group were to discuss the feasibility of data collection options, industry communication and collaboration, confidentiality issues, and metrics
- Implementation of a pilot project as a ‘proof of concept’ based on data that are currently collected in industry to define the feasibility, scope and barriers to ABU surveillance based on voluntary sharing of data.

The initial scope of activities has been to collect data on ABU in growing pigs (weaning to market) for the 2016 calendar year from a convenience sample of production systems willing to voluntarily share data. Retrospective data isare being obtained at a system level by product (both medically important and not medically important) and stratified by route (feed, water, injection) and where feasible by phase (e.g., nursery, finishing, wean-to-finish). These data will provide relatively basic estimates of ABU, but will still yield substantially more information than is currently available about ABU use in US swine. Seventeen systems have been contacted and or/visited and 11 (representing over 20% of national pig production) have agreed to provide the data requested. A process for managing data confidentially has been established, 4 systems have submitted data, and the remaining systems are expected to submit data over the next month. Initial reporting of summary data will occur among participants as soon as the data have been aggregated and analyzed. The next phase of the project will be to repeat the data collection for the 2017 year, and report the aggregate data for both 2016 and 2017 for the FDA is project in the fall of 2018. It is hoped that release of summary data to other industry stakeholders will occur prior to the FDA report but will be contingent on agreement of the participants. For all participants to date, no retrospective data are available on the purpose or details of administration (route, dose, duration). Obtaining data on these important aspects is a priority for the next phase of the work.

Keywords: Antibiotic, surveillance, measurement, resistance, metrics

Scientific Abstract:

The current crisis of antimicrobial resistance in human medicine has brought calls for improved antibiotic stewardship in all prescribing professions. Improved measurement of ABU is a universal component of improving stewardship. This project focused specifically on measurement of antibiotic use in the US swine industry. The initial objectives were to assess potential metrics of ABU in swine, and current sources of data and record keeping systems that could yield ABU data at relatively low cost. A further goal was to develop a framework to protect confidentiality of cooperating producers who might voluntarily share ABU data as part of a collaborative industry effort. An extensive review was conducted of systems to measure ABU that have been used previously in either research of surveillance settings in other countries, with the goal of designing and then implementing a pilot project to obtain ABU data in the US industry. In September 2016, the project was superseded by an extended (5 year) FDA funded project that was enabled by the activities undertaken in this NPB project.

To guide the design of a pilot project to obtain ABU data, initial activities involved industry communications and discussions centered on a task force convened by the NPB. Key issues identified were recognition of the deficit of knowledge about current ABU practices across the industry, prioritization of ABU in the breeding vs. growing phases of the industry, the need to further define appropriate metrics, and issues of confidentiality and handling of data. Based on these discussions, the scope of the initial year under the FDA project was to collect data on ABU in growing pigs (weaning to market) for the 2016 calendar year from a convenience sample of production systems that will voluntarily share data. Retrospective data are being obtained at a system level by product (both medically important and not medically important) and stratified by route (feed, water, injection) and where feasible by phase (e.g., nursery, finishing, wean-to-finish). These data will provide relatively coarse estimation of ABU, but still yield substantially more information than is currently available about ABU use in US swine.

Seventeen systems were contacted and/or visited and 11 (representing over 20% of national pig production) have agreed to provide the data requested. A process for managing data confidentially has been established, 4 systems have submitted data, and the remaining systems are expected to submit data over the next month. Initial reporting of summary data will occur among participants as soon as the data have been aggregated and analyzed. The next phase of the project will be to repeat the data collection for the 2017 year, and report the aggregate data for both 2016 and 2017 for the FDA is projected in the fall of 2018. It is hoped that release of summary data to other industry stakeholders will occur prior to the FDA report but will be contingent on agreement of the participants. For all participants to date, no retrospective data are available on the purpose or details of administration (route, dose, duration). Obtaining data on these important aspects is a priority for the next phase of the work.

Introduction:

The problem of antibiotic resistance in human clinical medicine is currently considered a global health crisis. Although the contribution of ABU in animals to the burden of antibiotic resistance in human medicine is greatly debated, and remains highly uncertain, it is not zero and therefore all veterinarians and animal producers have ethical obligations to use antibiotics as judiciously and effectively as possible.

FDA guidances 209/213 and the Veterinary Feed Directive, implemented by January 1, 2017, were a radical change in regulatory oversight of antibiotics in food animal production in the USA, and were implemented about 10 years after similar legislative changes in the European Union (EU). In this era of great concern about antimicrobial resistance, a core component of efforts to achieve better stewardship of ABU has been the need for improved measurement of ABU. European initiatives that have spurred calls for more surveillance of ABU in the USA were a 2011 EU directive calling for harmonization of methods for monitoring ABU in food animals, and in some countries further initiatives including mandatory and arbitrary reductions in ABU in food animals, and individual farm and veterinary level benchmarking of ABU. In the USA, data on ABU in food animals have been limited to national level sales data that has not included breakdown by species, and a limited number of cross-sectional research studies.

The current project was an initiative by the NPB to assess the potential for developing an industry driven system for obtaining estimates of ABU in industry. The project initially involved a review of prior approaches to measuring ABU in food animals in other countries. The second component of the project was to design and initiate a pilot project for obtaining data on ABU in the industry.

Objectives:

The project has three specific objectives related to measurement of ABU in the US swine industry:

1. Research and identify metrics that will provide value to the pork industry for continual improvement of antibiotic use practices.
2. Identify existing and/or new sources of data and record keeping systems to support the computation of metrics that will provide value to the pork industry.
3. Explore and develop a framework to protect anonymity and confidentiality of cooperating producers while providing data of sufficient granularity to achieve (a) and (b) above.

The specific outcomes anticipated for the project were:

1. White paper providing a detailed assessment of options for measuring ABU in the US swine industry, including feasibility assessment and relative costs.
2. Design of a pilot program based on the feasibility assessment.
3. Initial implementation of the pilot study of ABU.

Materials & Methods:

For Objectives 1 and 2, approaches to compiling current knowledge on measurement of antibiotic use (ABU) were:

1. *Review of published scientific literature and technical documents pertaining to measuring ABU in food animals*
Identification of relevant peer reviewed literature was conducted by a snowball method starting with a small number of key foundational papers and using the Web of Science citation index to identify related papers that cited the foundational papers, then in turn examining sources cited by, and citing, the identified papers. This was repeated iteratively to identify papers that addressed methodological aspects of collection and/or analysis of antibiotic use data in food animals. Technical documents were accessed from websites including AMCRA (Belgium), MARAN and SDa (Netherlands), DANMAP (Denmark), and ESVAC (EU).
2. *Updating practical knowledge of systems implemented internationally, focused on the EU, through visits to relevant stakeholders, including practicing veterinarians in Denmark, Belgium and The Netherlands*

A previous report on ABU measurement in EU countries was the outcome of a pork industry study to Europe in 2013. From March 14 to March 25, face-to-face meetings were held in Denmark, The Netherlands, and Belgium to better understand current developments in the collection and application of antibiotic use data. The meetings included groups involved in developing and administering ABU programs (Netherlands, Belgium, EPRUMA), researchers (Denmark, Belgium), and practicing swine veterinarians (Denmark, Netherlands, Belgium). Attendance on March 10, 2016, at a forum in Budapest, Hungary, on reducing antibiotic use enabled informal conversations with Dr. Martin Smith (UK swine industry), Dr. Gail Cunningham (Boehringer Ingelheim, Canada) both of whom are involved in ABU measurement issues in their respective countries. Dr. Davies also visited the largest swine practice in Australia (Chris Richards & Associates, Bendigo, Victoria, which serves clients throughout Australia and

South-east Asia) in December, 2015 to become familiar with a custom developed system for collecting ABU data electronically from client farms.

To obtain an initial assessment of the existence of retrospective data on ABU in the swine industry, personal visits to some large production systems, and administration of a survey to others, were conducted, and discussions were also held with industry benchmarking groups (AgriStats, Metafarms).

To guide the design of a pilot project to obtain ABU data, initial activities involved industry communications and discussions related to likely hurdles to establishment of a voluntary system for reporting antibiotic use in the US swine industry. Based on a recommendation in the April 2016 white paper, a specific task force was convened by the NPB, initially under the supervision of Dr. Jennifer Wishnie. Members of the committee included Dr. Davies, representatives of the NPB and National Pork Producers Council (NPPC), specialist swine veterinarians representing both integrated systems and clinics servicing independent farms, and swine producers (integrated and independent). Priority issues identified for the group were to discuss the feasibility of data collection options, industry communication and collaboration, confidentiality issues, and metrics. The group held a series of face-to-face meetings or conference calls follows:

Date	Event	Location
June 2, 2016	Face to Face meeting	Chicago
August 4, 2016	Conference Call	
August 31, 2016	Conference Call	
September 14, 2016	Conference Call	
November 16, 2016	Face to Face meeting	Kansas City

In April 2016, the FDA issued a Funding Opportunity Announcement directed at measurement of ABU in major food animal species. The NPB and NPPC encouraged the PI to submit a proposal to that FDA funding opportunity, which was submitted in May 2016. The FDA proposal, ultimately a combined proposal for the avian and swine industries, was submitted by Mindwalk Consulting, LLC (PI. Dr. Randall Singer, Co-PI. Dr. Davies) and was funded by FDA commencing in September 2016 with a projected 5 year duration (2016 – 2021). From that time, the FDA funded project has driven the ongoing evolution of the work initiated in project #15-186. However, this represents an expansion of the original scope of #15-186 rather than a fundamental change in direction. The goals specified in the FDA call were:

- *Provide detailed antimicrobial drug use data that accurately reflects actual on-farm use;*
- *Provide “baseline” data on antimicrobial use (i.e., data prior to the implementation of Guidance For Industry (GFI) #213*
- *Pilot methodologies for collecting, summarizing, and reporting antimicrobial use data;*
- *Foster public-private partnerships/collaboration;*
- *Leverage existing data systems and minimize burden and disruption to animal producers;*
- *Incorporate strategies for protecting farm/producer identity and other confidential information.*

Subsequent activities following the funding of the FDA project in September 2016 have involved confidential interactions between Dr. Davies and entities approached regarding the possibility of sharing data. This has been oriented towards larger production systems where retrospective data were more likely to be available. These efforts are ongoing given the projected 5-year duration of the FDA funded initiative, therefore the information provided in the Results section represents the *status quo* of that project as of October 2017. Another meeting of the NPB task force was held in Minneapolis on August 17, 2017, to discuss progress in the project and consider priorities for expanding the project in the second year.

Results:

The outcomes of the work on the first two objectives are presented in detail in Appendix 1, the white paper previously submitted to NPB in April 2016.

With respect to designing and implementing a pilot project, the outcomes of the NPB task force discussions are listed below:

- Recognition that there is a deficit of knowledge about current AMU practices across the industry. A key objective is to define current practices to enable benchmarking with the primary goal of assisting antibiotic stewardship. This should be achieved without the need for comprehensive, site-level measurement that would be resource intensive.
- Achieving data representative of the overall US swine industry is a desirable goal but will be difficult in a voluntary framework. Identification of likely sources of bias is a stated objective in the FDA proposal, but will not be an initial priority.
- Consideration of the needs of AMU surveillance in the breeding and growing phases of the industry, which are predominantly segregated in large systems. Both are considered important but growing pigs are a higher priority as they represent the bulk of the commercial swine population.
- The need to further define appropriate metrics in conjunction with the other major protein species. This is currently being addressed in ‘barnyard’ meetings (including representatives from FDA and USDA) to discuss preferred metrics for both qualitative and quantitative measures of stewardship.
- Compilation of a list of 47 antibiotic products most commonly used in swine categorized by route of administration and medical importance (per FDA GFI #152), and with information on label dose and duration where available.
- Discussion of issues of confidentiality and handling of data. Development of systems to ensure confidentiality of data is a required outcome of the FDA proposal. Models being explored in the poultry and ruminant industries were discussed. There was interest among the companies represented to consider involving AgriStats Inc., in the management of data as many potential participants currently use AgriStats services for benchmarking of production data, but data on ABU (other than cost) are not currently shared. Other companies (notably MetaFarms) also handle producer data confidentially and have potential to be similarly involved, and the potential for routine collection of AMU data is increasing with new technology options.

Due to the immediate need for a process to facilitate data sharing and analysis, Dr. Davies formed a limited liability company (Epitome Consulting LLC, Minneapolis, MN) for the specific purpose of aggregating and analyzing data provided by participants. Prior to sharing data, participating groups have establish non-disclosure agreements with Epitome Consulting to protect confidentiality.

Regarding the granularity of data, it was recognized that different levels of granularity of data can serve different purposes, and that different metrics may be more or less applicable different goals. Three general levels of granularity are outlined in Table 1 in relation to the purpose of data collection.

	Purpose	Scope	Metric
Level 1	Description	System	Weight
		Retrospective	
Level 2	Benchmarking	Sample sites	Animal Daily Dose?
		Retrospective	
Level 3	Stewardship	Sample sites Prospective	Used Daily Dose

Table 1: Outline of options for AMU measurement at different levels of granularity

At Level 1, retrospective data would be obtained at a system level by product (both medically important and not medically important) and stratified by route (feed, water, injection) and where feasible by phase (e.g., nursery, finishing, wean-to-finish). The primary metric is weight, with appropriate denominators being numbers of pigs marketed, or weight of product marketed (live or carcass). Level 1 data would provide relatively coarse estimation of ABU, but would be appropriate to describe trends in ABU over time by product class or drug and by route.

At Level 2, more granular data would be obtained retrospectively from random samples of sites within systems by phase (nursery, finishing, wean to finish). The primary purpose of Level 2 data would be to facilitate more meaningful benchmarking within and among systems by phase, and to quantify variability in ABU by phase. The primary metric would be a potency-adjusted measure similar to the animal daily dose metrics used in some countries in Europe, and the denominator would be based on animal time at risk (pig-days). The specific metrics should be developed in conjunction with the other protein industries in the barnyard group, but recognizing that the most useful measures may vary among industries. Level 2 data would provide much more specific description of ABU than Level 1, but calculated doses are estimates based on average ages, weights, and times of exposure for groups of pigs and therefore have significant limitations. Although this approach is used for regulatory purposes in some European countries, it does not capture actual usage regarding dose and duration. However, the feasibility of obtaining data is much greater than for level 3, and could be useful for broad industry benchmarking.

Measurement of actual antibiotic administration (Level 3) provides the greatest value for understanding ABU practices and supporting antibiotic stewardship initiatives. The preferred metric is ‘used daily doses’ that capture actual treatment events regarding drug, route, dose, and duration. This approach to date has primarily been used in research studies of limited scope due to the intensive nature of data collection and is not feasible with retrospective data as currently collected in the US industry. However, the potential for capturing actual use appears to vary between animal industries, and is becoming more feasible through development of technologies for automated collection of treatment data. Level 3 would require prospective data collection that would be much more intrusive for producers. Therefore, it is likely to be considered only on a limited scope in the latter part of the FDA project.

The goal for current efforts in data collection is to obtain retrospective Level 1 data for growing pigs (weaning to market) for the 2016 calendar year. Reporting will underline the limitations of weight as a metric without considering the relative potency of different antibiotic compounds. However, following acquisition of raw data on use, future adjustments for potency should be feasible as discussions on metrics across species are advanced. It is anticipated that collection of Level 2 data could be developed in the later

years of the FDA project, building on the data management and confidentiality structure implemented for Level 1.

These Level 1 data will provide relatively coarse estimates of ABU, but still provide substantially more information than is currently available about ABU use in US swine. Seventeen systems have been contacted and/or visited and 11 (representing over 20% of national pig production) have agreed to provide the data requested. A process for managing data confidentially has been established, 4 systems have submitted data, and the remaining systems are expected to submit data over the next month. Initial reporting of summary data will occur among participants when the data have been fully analyzed. The next phase of the project will be to repeat data collection for the 2017 year, and reporting of aggregate data for both 2016 and 2017 for the FDA is projected in the fall of 2018. It is hoped that release of summary data to other industry stakeholders will occur prior to the FDA report but will be contingent on agreement of the participants.

The NPB task force (August 17, 2017) discussed several options for obtaining further data in the second year of the project, including expansion to include sow herd data, recruitment of more herds, obtaining of more historic data, and data on purpose and administration. The last option was considered to have highest priority as available data records amounts of antibiotics used, but not the purpose or details of administration (route, dose, duration). This information would greatly enhance understanding of how antibiotics are being used and would have value for veterinary and producer education. Consequently, a survey is being developed (based on a survey previously used for AASV members) to obtain this information from both participating systems and across the wider swine veterinary profession.

Discussion:

Pressures to measure ABU in food animals are converging from multiple sources including international and national agencies, groups opposed to animal production, competitive pressures from other countries and other meat industries within the USA, and from downstream customers in the food industry. Increasingly, there are emerging market based initiatives to differentiate products (e.g., 'antibiotic free', 'raised without antibiotics', 'no antibiotics ever', etc.) or to ensure customers that ABU is appropriately managed in the supply chain. In this dynamic situation, there are obvious risks to all industries if ABU is positioned as a competitive issue. Antibiotics remain important tools for protecting animal health and welfare in animal production, and undesirable consequences could occur if measurement of ABU becomes a competitive platform, and particularly if metrics used do not capture appropriateness of use or reflect selective pressures that translate into human health risks. Development of appropriate metrics is thus central to meaningful assessment of ABU, yet current metrics all have shortcomings. The pros and cons of options for metrics are overwhelmingly driven by definition of purpose. Although there appears to be a strong appetite for comparing ABU across countries and industries, this is highly unlikely to be of any substantial benefit given the biological differences among species and the variability in disease risks that exist among regions and countries. ABU measurement has the greatest potential to be of value by enhancing understanding of practices and trends within individual species and geographic settings, with a focus on antibiotic stewardship and education. In this context, cooperation among otherwise competing companies ('coopetition') regarding ABU should be encouraged. This appears to be understood by many members of the industry and is reflected in current willingness of companies to participate in this initiative.

This project remains in its early stages, and has progressed more slowly than desired. This may be due to the sensitivity of the issue and the need to carefully consider participation, understandable uncertainty about the confidentiality of the process, logistic difficulties and costs in time and personnel to extract the necessary data, competing pressures in businesses, and likely other considerations. However, it is expected that momentum will be increased after the first round of data collection and analysis is completed over the next 2 months. This should

provide a foundation of process, and greater confidence regarding confidentiality. Although the initial focus of work has been to develop an infrastructure for voluntary sharing of ABU that could indicate trends in ABU, enhancement of that information with data on the purpose and practices of administration of antibiotics would add great value and will be a focus of the next phase of the work. The PI will continue to work with the NPB task force to guide the direction of the work over the coming years.

APPENDIX 1

Approaches for Measuring Antibiotic Use in the US Swine Industry

Dr. Peter Davies, BVSc, PhD

Introduction

The urgency to address antibiotic resistance in human medicine is echoed among health oriented entities at local, national and international levels. Bacterial genes that confer resistance to antibiotics are an ancient phenomenon and are widely distributed in nature, yet it is generally accepted that antibiotic use is the primary selective force behind the emergence of resistant bacteria that are clinically problematic. Therefore, optimizing strategies for antibiotic use ('stewardship') is an essential component of efforts to combat clinical resistance.

At an ecological level, antibiotic use in all arenas (human, food animal, companion animal, aquaculture, apiculture, agriculture,...) will contribute to some extent to the global aggregate of resistant bacteria, albeit with different clinical consequences. The unequivocal link for resistance between food animal populations and the general human population is foodborne transmission of zoonotic pathogens, most notably *Salmonella* and *Campylobacter*, while the relative importance of other potential pathways and organisms is less certain. The relative contribution of antibiotic use in food animals to clinical resistance in human medicine remains uncertain and endlessly debated, but is not 'zero'. Therefore, veterinarians and food animal producers have a responsibility to optimize use of antibiotics such that they employ 'as little as possible' but as 'much as necessary' to maintain animal health and welfare, and the safety and security of the food supply.

Optimization of antibiotic use requires measurement. Antibiotics have been available for use in animals for over 60 years, but systematic efforts to measure antibiotic use in animals at a national scale are a relatively recent undertaking. Data on gross sales of antibiotics by country are reported in several countries including the USA, but generally lack sufficient granularity to allow meaningful assessment of usage or to inform antibiotic stewardship efforts. The goal of this review is to consolidate current knowledge and practices being employed to measure antibiotic use in food animal production, with an emphasis on swine. The scope of the review also includes evaluation of the strengths and weaknesses of metrics that have been employed in quantifying antibiotic use. It also reviews existing programs used to quantify antibiotic use in other countries and considers several options for developing such a system for the US swine industry.

Methods

Two key approaches to compiling current knowledge on measurement of antibiotic use (ABU) were:

1. *Review of published scientific literature and technical documents pertaining to measuring ABU in food animals*

Identification of relevant peer reviewed literature was conducted by a snowball method starting with a small number of key foundational papers and using the Web of Science citation index to identify related papers that cited the foundational papers, then in turn examining sources cited by, and citing, the identified papers. This was repeated iteratively to identify papers that addressed methodological aspects of collection and/or analysis of antibiotic use data in food animals. Technical documents were accessed from websites including AMCRA (Belgium), MARAN and SDa (Netherlands), DANMAP (Denmark), and ESVAC (EU).

2. *Updating practical knowledge of systems implemented internationally, focused on the EU, through visits to relevant stakeholders, including practicing veterinarians in Denmark, Belgium and The Netherlands*

A previous report on ABU measurement in EU countries was the outcome of a pork industry study to Europe in 2013 (Appendix 1). From March 14 to March 25, face-to-face meetings were held in Denmark, The Netherlands, and Belgium to better understand current developments in the collection and

application of antibiotic use data (a separate report of these meetings will be submitted separately). The meetings included groups involved in developing and administering ABU programs (Netherlands, Belgium, EPRUMA), researchers (Denmark, Belgium), and practicing swine veterinarians (Denmark, Netherlands, Belgium). Attendance on March 10, 2016, at a forum in Budapest, Hungary, on reducing antibiotic use enabled informal conversations with Dr. Martin Smith (UK swine industry), Dr. Gail Cunningham (Boehringer Ingelheim, Canada) both of whom are involved in ABU measurement issues in their respective countries. Dr. Davies also visited the largest swine practice in Australia (Chris Richards & Associates, Bendigo, Victoria, which serves clients throughout Australia and South-east Asia) in December, 2015 to become familiar with a custom developed system for collecting ABU data electronically from client farms.

The following discussion attempts to integrate the information gathered into a narrative to inform options for measuring antibiotic use in the US swine industry.

Approaches to Measurement of Antibiotic Use in Food Animals

Antibiotics have been available for use in animals for over 60 years, but systematic efforts to quantify antibiotic use at the national level have mostly evolved over the last 20 years. Analysis of national sales data has been, and remains, the predominant approach, but has recognized limitations that have driven efforts to obtain more granular data. The motives for calls for more detailed data on ABU are diverse and include:

- World Health Organisation policy to standardize protocols to facilitate global harmonization in surveillance of ABU in humans and animals, and of antibiotic resistance (http://www.who.int/world-health-day/2011/presskit/whd2011_fs4d_subanimal.pdf?ua=1)
- European Union directive to harmonize antibiotic use surveillance across countries as part of the Action plan against the rising threats from Antibiotic Resistance (http://ec.europa.eu/dgs/health_food-safety/docs/communication_amr_2011_748_en.pdf)
- Calls for better surveillance of antibiotic use in food animals as part of the National Action Plan for Combatting Antibiotic Resistant Bacteria (https://www.whitehouse.gov/sites/default/files/docs/national_action_plan_for_combating_antibiotic-resistant_bacteria.pdf)
- US Government agencies seeking to gauge the impact of regulatory changes to antibiotic use, specifically FDA guidances 209/213
- Consumer groups/ politicians seeking stricter regulation and monitoring of AMU in food animals to underpin stewardship (e.g., the Delivering Antibiotic Transparency in Animals Act)
- Specific initiatives in some EU countries (Denmark, Netherlands, Belgium) to monitor and benchmark AMU at the end user (farm, veterinarian) level
- Growing demands from downstream customers for assurances related to judicious antibiotic use in the supply chain
- Scientists advocating the need for reliable ABU data to enable meaningful risk assessment of the impact of antibiotic use in food animals on human health. (McEwen and Singer, 2006)

Numerous sources have elaborated on the challenges involved in quantifying antibiotic use (ABU) in food animal populations. (Chauvin, et al., 2001; Jensen, et al., 2004; Chauvin, et al., 2008; European Medicines Agency, 2015) Meaningful metrics of ABU requires consideration of both the numerators (measures of quantifying use) and the denominators (specifying the relevant populations and time). General approaches and metrics are summarized in Table 1, indicating key references.

Table 1: Overview of approaches to quantify antibiotic use in animals

Approach	Key References
Financial cost	Chauvin et al. (2001, 2008)

Weight (active compound)	Grave et al. (2010)
Animal daily doses	Jensen et al. (2004)
Animal course doses	European Medicines Agency (2015)
Prescribed daily dose	Pardon et al. (2012)
Used daily doses/kg-pig	Callens et al. (2012)
Used course doses	Menéndez González et al. (2010)
% of herds using specific antibiotics	Jordan et al. (2009)

Financial cost

Quantification based on financial parameters was the basis of most early efforts to quantify drug use at a population level.(Capellà, 1993) Currently in the US, benchmarking of animal health costs (which may include antibiotics, vaccines and other expenditures) is commonly conducted within or among (e.g., Agri Stats) production systems for reasons other than understanding patterns of antibiotic use (ABU). Measurement of ABU in financial terms is problematic as it ignores variability in costs of different active substances or products, and also that costs on a unit basis may vary between groups being compared (particularly among countries) and over time (Chauvin at al., 2001, 2008). In addition, it does not provide sufficient granularity to understand patterns of use and trends can be shaped by economic factors in addition to patterns of use. Retrospective analysis of costs of ABU in the more integrated segment of the US swine industry could provide some insight into recent trends (5-10 years) in ABU, but the price-related uncertainties inherent in the data would likely lead to minimal insight into usage patterns.

Weight of active ingredients

Measurement of the gross weight (typically of the active ingredient) has been the mainstay of most national recording of ABU in animal populations. Many developed countries have legislation [e.g., Animal Drug User Fee Act (ADUFA) in the USA] that requires pharmaceutical companies to report sales of antibiotic products registered for use in food animals, and weight is typically the standard measure of reporting for most products. (Grave, et al., 2014; Food and Drug Administration, 2015). Although gross figures on weight of antibiotics used are frequently highlighted in the media, the measure has significant shortcomings as a measure of ABU at a population level. Beyond the limitation that sales data indicate distribution rather than actual use, there are significant technical concerns related to definition of compounds to be included, their relative potency, and definition of the population(s) at risk. Notably, no meaningful indication of the selective pressure associated with ABU is obtained without consideration of the relative potency of different compounds.(Chauvin, et al., 2001)

Both financial and weight measures of ABU are effectively meaningless without explicit denominator(s) for the population(s) at risk. The simplistic approach to ignore population demographics to compare gross weights of ABU in the human and animal arenas is prevalent in the media and among critics of animal production. The fallibility of this approach is demonstrated in a French study where total ABU in veterinary medicine (1320 tonnes) was 1.7 times higher than in human medicine (760 tonnes).(Moulin, et al., 2008) However, when expressed on a demographic basis using the estimated weight of the animal and human populations, ABU was almost 3 times higher in humans (220 mg/kg/yr) than in animals (80 mg/kg/year), and there were substantial differences in the main classes of antibiotics used in animals (mostly tetracyclines and sulfonamides) and human medicine. Similar patterns have been reported by others,(Ungemach, 2000; Murphy, 2015) and denominator issues in quantifying ABU are considered in more detail below.

The relative importance of other limitations of weight measures depends on the purposes for which the data are to be used. Both the WHO and FDA have defined lists that differentiate antibiotics with respect to their importance in human medicine, and the latter list informed FDA guidances 209 and 213 being implemented in the USA. The most recent (2014) US data show that 38% of the weight of ABU reported under ADUFA was for products deemed not to be medically important, (Food and Drug Administration, 2015). Of these, 80% by weight were ionophores which are not included as antibiotics in the EU surveillance.(Grave, et al., 2014) A desirable outcome of the legislative changes in the USA would be a shift

of ABU away from medically important antibiotics to compounds that are not medically important. The effects of such a change on gross weight of ABU would be influenced by the relative potencies of the products substituted. This underlines the need to stratify ABU data with respect to medical importance and product class, and preferably to derive measures that adjust for potency (see section on potency adjusted measures below).

Currently, a major limitation of sales data in Europe and the USA relates to the distribution of products across animal species. In most countries including the USA, many antibiotics are labeled for use in multiple animal species, and sponsors are not required (or indeed able) to provide sales data by animal species. Therefore the data are aggregates for all species listed on approved labels, in some cases combining sales for both food animal and non-food animal species (e.g., companion animals) in unknown proportions. (Food and Drug Administration, 2015) In the USA, the AMDUCA and MUMS legislation provide a legal basis for extra-label drug use in food animals, whereby products labeled for use in one species (including human products) can be used in other species when specific conditions are met.

In Europe, where coordinated efforts to harmonize surveillance of ABU in animals have been underway via the European Surveillance of Veterinary Antibiotic Consumption (ESVAC) since 2009, difficulty in discerning use among food animal and other species remains an obstacle to interpreting sales data. (Grave, et al., 2014). Differences exist among countries in the demographics of species that are included in sales data (e.g., horses are considered as food animals in the EU and included in sales data, and fish may be included in some countries but not others). Furthermore, doses of particular antibiotics may differ substantially among species, therefore the relative size of food animal industries across countries will confound interpretation of sales data at a national level. (Grave, et al., 2014) ABU can vary markedly between industry sectors even within species, such as cattle (dairy, veal, cattle at pasture, fed cattle), (Merle, et al., 2012) and poultry (broilers, layers), due to differences in prevalent pathogens, lifespan, and production conditions. Consequently, simple comparisons between countries, even within a species, are likely to be uninformative or even invalid whenever differences in industry demographics are not accounted for.

A recent detailed analysis of ABU data from Denmark and the Netherlands (countries at the forefront of measuring ABU in food animals) concluded that simple country comparisons based on total sales figures ‘entails the risk of serious misinterpretations’. (Bondt, et al., 2013) Notably, differences in exposure among animal species were much higher than the overall difference between the two countries, and the analysis found estimates were strongly influenced by animal demographics and gave ‘very inaccurate indication of the true differences in exposure per animal species’. (Bondt, et al., 2013) It was concluded that it is absolutely necessary to have species specific data to assess variation in antibiotic exposure between countries.

However, due to the difficulty in obtaining reliable species specific data, ‘sales data as a proxy for consumption will continue to be collected for the foreseeable future as the core ESVAC activity, even whilst work is carried out to develop systems to collect data on actual consumption of antibiotics per species’. (European Surveillance of Veterinary Antimicrobial Consumption, 2016) This recent draft statement of the ESVAC vision points out the ‘extremely resource-demanding nature of work to collect data by animal species’. For this reason ESVAC has narrowed the scope of its efforts to obtain species specific data to 3 groups (cattle, swine, and poultry). It is now, 7 years after being formed, developing guidelines for the collection of harmonized and standardized data on consumption by species and to define the populations ‘at risk of treatment’. (European Surveillance of Veterinary Antimicrobial Consumption, 2016) Importantly, based on experiences to address species level collection, the report states ‘the highly resource demanding ‘manual’ collection of data on consumption per species at national level suggests that it would not be a sustainable approach in the long term. Therefore, the focus for ESVAC will be on automated or semi automated data collection, preferably covering all farms or, alternatively, from a representative number of farms.’ (European Surveillance of Veterinary Antimicrobial Consumption, 2016)

Denominator issues – defining the population at risk

Meaningful measurement of any population parameter is dependent on clear definition of a relevant denominator(s). This is not a trivial problem as the relationship between the inventory (and biomass) of food animals in a population (i.e., population existing at a point in time) and the number of animals raised over a defined period varies widely among animal species. For example, the US swine population is comprised of approximately 6 million sows and 60 million growing pigs but approximately 110 million animals are marketed annually due to the growing period of about 6 months. These relationships vary enormously from beef cattle (around 20-22 months growing period) and broilers (6-9 weeks growing period). The apparent intensity of ABU among species would therefore vary markedly depending on whether the choice of the 'biomass' denominator was based on the animal inventory or the annual production.

ESVAC has attempted to address this problem by developing a standardized approach to defining the population denominators, termed the population corrective unit (PCU).(Grave, et al., 2014) The PCU for each 'animal category', acknowledged as a 'proxy for biomass', is calculated by multiplying numbers of live animals (dairy cows, sheep, sows and horses), and slaughtered animals (cattle, pigs, lambs, poultry and turkeys) using a standardized weight being "the time most likely for treatment". However, due to data restrictions, for farmed fish the biomass slaughtered in each country was used for the PCU.(Grave, et al., 2014) This approach may constitute a reasonable compromise to achieve standardization of the population denominator among countries, but has inherent limitations in comparing ABU among species (as different proxies for biomass are used) and even within species (sow vs. growing pigs). Again, the differing needs for ABU among different species (due to different biology and pathogen profiles) means that species demographics will confound overall measures of ABU at the national level whenever species specific data are not available.

Potency (dose) adjusted measures

As indicated above, the inadequacy of weight as a meaningful 'numerator' measure of ABU is primarily related to the large variability in potency among antibiotics. Substitution of a less potent compound (e.g., tetracyclines) by a more potent compound (e.g., cephalosporin) would result in an apparent reduction in ABU based on weight, when in reality the intensity of ABU (in terms of doses) could be unaltered or increased.(Jensen, et al., 2004) The accepted approach to this problem, instituted by the WHO to facilitate comparison of drug usage among countries, is to use a divisor to convert the weight of compound to a dose related measure termed the defined daily dose (DDD). This converts the crude mass of product used in a setting to a standardized number of daily doses which can be expressed with the denominator of choice (e.g., population at risk, or hospital-bed-days) to create numeric estimates of drug use in the populations of interest. Although simple in concept, the application in DDD in practice has some caveats listed by the WHO (http://www.whooc.no/ddd/definition_and_general_considera/) including:

- DDD is a unit of measurement and does not necessarily reflect the recommended or prescribed daily dose.
- Doses for individual patients and patient groups will often differ from the DDD and will necessarily have to be based on individual characteristics (e.g. age and weight) and pharmacokinetic considerations.
- Drug consumption data presented in DDDs only give a rough estimate of consumption and not an exact picture of actual use.
- DDD is often identical for various dosage forms of the same drug. Different DDDs may be established when the bioavailability is substantially different for various routes of administration (e.g. oral and parenteral administration) or if the dosage forms are used for different indications.
- The DDD is nearly always a compromise based on a review of the available information including doses used in various countries when this information is available.
- The DDD is sometimes a dose that is rarely if ever prescribed, because it is an average of two or more commonly used dose sizes.

The DDD approach has also been adopted in animal populations, but not necessarily in a uniform manner (Jensen, et al., 2004; Merle, et al., 2014) and the nomenclature applied has been inconsistent and somewhat confusing. It is noted that the caveats related to the use of DDD by the WHO are also relevant to the use of this approach in animal populations, and particularly for international comparisons. In principle, daily dose conversions should be defined for each product, formulation, species, and route of administration, and compromise values will be required for products that have more than one label dose for different diseases within a species. The specifics can also vary over time within a country. In Denmark, the “animal daily dose” originally defined in 2003 was updated after 2013 with the “Defined Animal Daily Dose” due to refinement based on routes of administration. The Dutch values are available on line and are ‘regularly updated’ (<http://www.autoriteitdiergeenemiddelen.nl/en/dg-standard>). For purposes of illustration, a section of the DADD values used in the DANMAP 2014 report is shown in Figure 1. Note that while values are expected to differ widely between compounds (the purpose for adjusting weights) they also can vary on the preparation and route of administration of an individual drug. Table 2 lists a selection of terms and definitions that have been applied in published work on quantifying ABU. A study of the impact of the methods used between Denmark and the Netherlands concluded that the differences had substantial influence on the results of antibiotic consumption in pigs. Therefore harmonized units of measurement, animal weights and animal (sub) categories would be necessary to enable international comparison of ABU data. (Taverne, et al., 2015)

The variability in terminology and abbreviations in publications from various groups is confusing. However, although varying in details, the underlying calculations are rather generic with the following key components:

- 1) For the numerator, weights are converted to account for potency based on consensus values derived from product labels (ADD, DADD, on either actual doses used, or less commonly based on actual use or based on doses indicated in written prescriptions.
- 2) The number of ‘daily doses’ is expressed over a defined period (typically one year) in relation to some denominator representing the biomass of animals treated.
- 3) Typically, the proxy measures for biomass are purposively chosen as reasonable estimates for animals in the respective stages of production (sows, piglets, nursery, finishing). The values used are not necessarily standardized among countries.
- 4) A further consideration is the duration of action of single treatments together with the recommended duration of treatments using multiple administrations. This may be addressed by converting long-acting treatments to daily dose equivalents or comparing treatments in terms of courses rather than daily doses.

Figure 1: Subset of the Defined Animal Daily Dose values use to adjust weights of antibiotics used for potency in DANMAP

(http://www.danmap.org/~media/Projekt%20sites/Danmap/DANMAP%20reports/DANMAP%202014/Danmap_2014.ashx)

ATCvet code	Active compound	Administration route	Pharmaceutical form	DADD (mg/kg)
QA07AA01	Neomycin	Peroralt	soluble powder	14.0
			solution	85.0
QA07AA06	Paromomycin	Peroralt	soluble powder	22.8
QA07AA10	Colistin	Peroralt	soluble powder	3.3
			oral solution	3.3
QA07AA90	Dihydrostreptomycin	Peroralt	soluble tablet	25.0
QA07AA91	Gentamicinsulfat	Peroralt	oral powder	2.0
QA07AA92	Apramycin	Peroralt	premix	5.0
			soluble powder	10.0
			oral powder	5.0
QJ01BA90	Florfenicol	Parenteralt	injection	7.5
		Peroralt	solution	10.0
			oral solution	10.0
			oral powder	10.0
QJ01BA99	Florfenicol	Parenteralt	injection	7.5
QJ01CA01	Ampicillin	Parenteralt	injection	15.0
QJ01CA04	Amoxicillin	Parenteralt	injection	15.0
		Peroralt	premix	15.0
			soluble powder	17.5
			oral powder	15.0
QJ01CE01	Benzylpenicillinkalium	Parenteralt	injection	9.4
QJ01CE02	Phenoxymethylpenicillin	Peroralt	soluble powder	10.0
QJ01CE09	Benzylpenicillinprocain	Parenteralt	injection	15.0
QJ01CE90	Benzylpenicillin	Parenteralt	injection	8.9
QJ01CR02	Amoxicillin	Parenteralt	injection	7.0
		Peroralt	soluble powder	20.0

Table 2: Examples of terminology used with potency adjusted measures of ABU in animals

Author*	Country	Terminology (abbreviation)	Comment
Jensen et al (2004)	Denmark	Animal defined daily doses (ADD)	Conversion of weights to doses based on consensus for specific compounds and species
DANMAP 2014	Denmark	Defined Animal Daily Doses (DADD)	Updated values based on routes of administration
		Defined Animal Population Dose (DAPD)	DADD per 1000 animal days
Merle et al (2013)	Germany	Defined Animal Daily Doses (ADD)	Dose per animal and day calculated from recommended dosages and estimated live weights
		Used Daily Doses (UDD)	Dose derived from records of actual administration
Speksnijder et al (2015)	Netherlands	Defined doses per animal year (DDDY)	
Pardon et al (2012)	Belgium	Prescribed daily dose (PDD)	Prescription dose divided by mean live weigh of animals
Callens et al. (2012)	Belgium	Used daily doses/kg-pig (UDD)	
AMCRA	Belgium	BD100	Daily dose per 100 animal days
Sjolund et al (2015)	Sweden	Treatment Index (TI)	Defined daily doses expressed as treatments per 1000 animal days
Van Rennings et al. (2015)	Germany	Treatment frequency (TF)	<u>Used Daily Doses</u> Population size
Menéndez González et al. (2010)	Switzerland	Multiple measures including used daily dose, used course dose, and treatment incidence.	
ESVAC	EU	Defined daily dose for animals (DDDvet)	Assumed average dose per kg animal per day for a species
		Defined course dose for animals (DCDvet)	Assumed average dose per kg animal per treatment course for a species

* More than one method is used in several of these sources

It is likely that future efforts in the USA to quantify ABU in food animals will (and arguably should) adopt potency adjusted measures instead of weight. However, this is not a trivial undertaking and there are inherent tradeoffs in developing values that are most appropriate for a given national industry (i.e., aligned closely with actual doses used) and with the ability to perform international comparisons (as acknowledged by the WHO for human ABU). To address this in Europe, ESVAC introduced specific terms (DDDvet, DCDvet) and recommended that the terms be reserved for the ESVAC units to avoid confusion with similar units used by other groups in individual countries. They also recommended that this system be used to report national data in the EU. To indicate the scope of this undertaking, there were 2,228 unique products for oral and injectable use (broiler, cattle or pigs) with information on daily dose and number of treatment days for single substances, and a further 662 products with active substances in combination. (European Medicines Agency, 2015).

Assuming the core goal of measuring ABU is to support stewardship efforts and monitor usage trends in industry, priority should be given to country specific methods that more closely reflect usage. That is, it is more important to use methods that provide a more accurate assessment of patterns of ABU and trends over time in the USA than to use international methods to facilitate international comparisons. For example, one particular feature of US production is the considerable proportion of pigs raised in wean-to-finish facilities, for which no EU country has yet developed a standard weight measure (as few such facilities exist). It would be therefore necessary to define of a 'standard weight' for wean to finish pigs, as well as nursery and finishing pigs. It should be recognized that one limitation of this defined dose approach (i.e., that actual doses used in pigs much smaller or larger than the standard weight are incorrectly estimated) would be magnified in wean-to-finish barns due to the large weight range (e.g. 12 to >260lbs). Daily doses for treating weaned pig diseases would be greatly underestimated by using a mid-range weight (e.g. 120 lbs), whereas daily doses administered to heavier pigs later in the finishing would be overestimated.

In summary, adoption of the defined daily dose approach should be encouraged due to its superiority over gross weight measures. The development of the relevant conversion factors should be based on US labels and practices and in the context of US production systems with respect to preferred population denominators. This will be a considerable undertaking which needs to be discussed among other food animal industries and relevant government agencies.

Overview of options for ABU surveillance in the US swine industry

Programs to capture national level data on antibiotic use in food animals can be grouped into 3 general categories

- Comprehensive programs aiming to capture data from most or all producers and veterinarians for benchmarking and intervention at the enterprise or individual level
- Sample based programs that seek to determine trends in usage based on representative samples of herds and flocks and that are maintained over time
- Research based efforts that are generally not sustained over time

Comprehensive programs

Denmark, the Netherlands, Belgium, and Germany have developed relatively comprehensive programs to quantify ABU in food animals including swine. The overall structure and operations of these programs were described in the report from the 2013 study tour (Appendix 1). Some of the key features of these programs include:

- The programs have been directed by expert committees representing diverse stakeholders from government, industry and academia. These groups, such as The Netherlands Veterinary Medicines Authority (<http://www.autoriteitdiergezondheidsmiddelen.nl/en/home>) and AMCRA in Belgium (<http://www.amcra.be/en>) include paid permanent staff and serve as a focus for information exchange, planning and communications on ABU surveillance and related issues.
- Funding for the programs is not fully transparent but has involved contributions from multiple stakeholders including government and industry, and in some cases from the veterinary profession.
- There is a legal basis requiring stakeholders to report ABU as stipulated in the respective programs.
- All programs have invested in comprehensive systems for data collection that enable data to be either captured directly from other data repositories (e.g., pharmacies or veterinary practice management software) and enable direct data entry via the internet. In some cases, the systems are interactive and enable producers and veterinarians to view their status for ABU relative to the broader industry via the internet.
- The programs are designed to quantify use at the individual farm and veterinarian level, and use statistically derived distribution to identify high users for interventions on a percentile basis. The general approaches are the same, although details, such as the time frames for analysis and cut-offs used for categorizing farms or veterinarians, vary.
- In these countries, growth promotants have been unavailable since at least 2006 (2000 in Denmark) and all antibiotics are used under veterinary oversight (i.e., prescription only).
- In Denmark, veterinarians cannot sell the antibiotics they prescribe (apart from emergency treatments), and data collection is automated from pharmacies, feed mills and veterinarians. In non-Scandinavian countries, veterinarians retain the right to sell antibiotics and also play a central role in provision of data to the programs. It appears there is a considerable administrative burden on veterinarians that is not explicitly considered as a cost of the programs.
- Programs including penalties for high use have not yet imposed severe restrictions on producers. Since introducing the 'Yellow Card' program in 2011, no Danish producer has been issued a 'Red Card' with associated penalties (Jan Dahl, personal communication March, 2016). This is also the case in the Netherlands but the program has been in place for less time (Hetty van Beers, personal communication, March 2016).

- In the Netherlands, in addition to the surveillance system, the government mandated arbitrary reductions in ABU as targets for the industry.
- In the countries visited, abolition of routine preventive uses of antibiotics is being pursued, although ‘metaphylaxis’ will continue to be permitted. A measure to ban preventive use of antibiotics in food animals was recently introduced into the European parliament but has not yet become law.

These programs represent the ‘state of the art’ in ABU surveillance globally, but are expensive and complex programs that to date have not been replicated in most European countries, and this appears likely to remain the case into the future. (Grave, et al., 2014; European Surveillance of Veterinary Antimicrobial Consumption, 2016) As such, they are not considered to be feasible models for the US industry in the foreseeable future. However, it is anticipated that some consumer groups will advocate for the implementation of a comprehensive program.

In Great Britain, as of April 2016 a subgroup of the Pig Health and Welfare Council (<http://pork.ahdb.org.uk/health-welfare/pig-health-welfare-council/>) tasked with measuring and optimizing ABU in the pig industry has also developed a system (Pig Industry Medicines Hub) for collecting data on antibiotic level which is in the early stages of implementation (Martin Smith, personal communication, March 2016). Unlike the multispecies systems mentioned previously, the British system was developed by and for the pig industry, in collaboration with the government agency overseeing veterinary medicines, as an on-line database for recording all antibiotic use. It was designed to be compliant with existing quality assurance programs in the UK and to enable sharing data with ESVAC in Brussels.

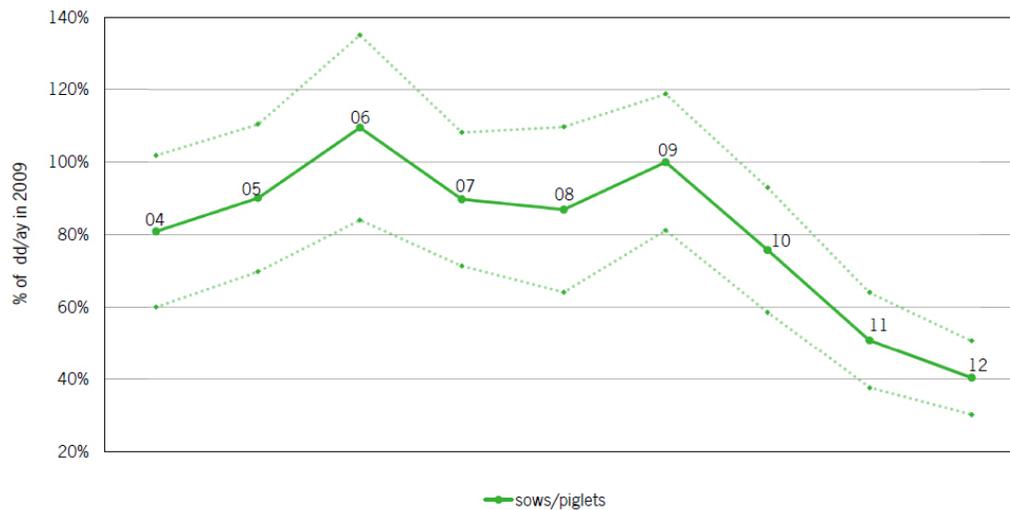
Sample based programs

If the key purpose of ABU surveillance is to quantify trends and patterns over time, including responses to regulatory or educational interventions, the comprehensive ‘census’ approach is not necessary and measurement of ABU at a regional or national level can be achieved with conventional population sampling approaches. The appeal of sample based programs is that representative population data can be obtained at relatively low cost. However it is important to clearly define the required precision of the program, the frequency with which data will be collected and analyzed, and the level of detail required in data collected from sampled farms.

The best example of a long-term, sample-based surveillance program for ABU in food animals is the MARAN program in the Netherlands (<http://www.wageningenur.nl/en/Research-Results/Projects-and-programmes/MARAN-Antibiotic-usage/Materials-methods/Survey-data-and-statistical-analysis.htm>).

Briefly, a stratified random sampling method is used to select farms from within a network of 1,500 farms (not just animal production), and each year a new sample of farms is selected. Stratification is based on farm size and species, and routinely includes swine, cattle and poultry farms. Data on all antibiotic use and veterinary services are recorded on the selected farms. ABU in each species is estimated at the national level as mean daily dosages per ‘average animal present on an average farm’, using weighting to adjust for the stratified sampling. The data are analyzed separately for breeding (typically farrow-to-feeder pig) and fattening (finishing) farms and published with confidence limits to indicate the uncertainty in the national estimates (Figure 2). Detailed data are also published for individual antibiotics

Figure 2: MARAN: 2012 report on trends in antibiotic use in breeding farms (2009 base)



The number of swine farms sampled annually in the MARAN program has been of the order of 40 to 50 sow farms and 50 to 80 fattening farms annually. The costs of the program are unknown, and likely difficult to determine as it is nested within a much broader project designed for economic analyses in agriculture. As a stand-alone program in the USA, apart from the costs, obtaining participation from randomly selected producers is likely to be a substantial barrier to executing such a program. However, the program illustrates that with appropriate design, representative and detailed ABU data at a national level could be obtained using a sample based program.

In the USA, the National Animal Health Monitoring System (NAHMS) has used such a sample based approach to assess diverse parameters of health and production in food animal species in the USA. Similar to MARAN, a stratified sampling approach is used to obtain a representative sample of farms across the major swine producing states. Estimates of antibiotic use in feed for growing pigs derived from the 2006 NAHMS survey were published in 2012. The study was cross-sectional but involved 2 farms visits and data were collected from over 500 farms for a 6 month period. (Apley, et al., 2012) However, typically major species such as swine are studied by NAHMS approximately every 5 years, and priorities for inclusion in each round are developed with industry and tend to shift over time. Clearly, more frequent and comprehensive sampling is required to document patterns of ABU in the industry over time. Budget requests by the USDA to implement expanded programs for ABU surveillance in accordance with the National Action Plan to date have not been successful.

Research based programs

There have been numerous research publications from various countries which have reported data on ABU patterns in various animal industries. The distinguishing feature of such work is that it is typically ‘snap shot’ data which has some informative descriptive value but does not enable reliable assessment of trends. The current expectations for surveillance of ABU in food animals in developed countries, including goals of the National Action Plan in the USA, are of a scope beyond what can be achieved with ad hoc research efforts. Conversely, implementation of a more robust and comprehensive surveillance capability would likely generate new opportunities for research into antibiotic use and resistance.

FDA attributes of a surveillance program for ABU in food animals

In its recent Funding Opportunity Announcement (<https://grants.nih.gov/grants/guide/rfa-files/RFA-FD-16-046.html>) the FDA outlined features are considered desirable to meet its overall goals to (1) provide needed information on antimicrobial use practices in various animal production settings (i.e., cattle, swine, and poultry) and 2) provide important information on data collection methodologies to help optimize long-term strategies for collecting and reporting such data. Features listed were:

- Provide detailed antimicrobial drug use data that accurately reflects actual on-farm use;

- Provide “baseline” data on antimicrobial use (i.e., data prior to the implementation of Guidance For Industry (GFI) #213, which asked pharmaceutical companies to voluntarily revise the FDA-approved use conditions on the labels of medically important antimicrobials in feed & water.);
- Pilot methodologies for collecting, summarizing, and reporting antimicrobial use data;
- Foster public-private partnerships/collaboration;
- Leverage existing data systems and minimize burden and disruption to animal producers;
- Incorporate strategies for protecting farm/producer identity and other confidential information.

It was also listed that projects to be supported for cattle, swine or poultry should 1) provide information including drug name, dose, duration of use, purpose of use, and quantity/extent of use; 2) provide for annual collection and reporting of antimicrobial use information, including for the 2016 calendar year; and 3) characterize the extent to which the collected data are representative of the particular relevant industry segment in the US.; and 4) produce an annual summary report of the data collected, including a detailed description of the data collection methodology.

It is unlikely that in the absence of substantial government funding to support a stand-alone comprehensive program such VetStat in Denmark, any single initiative will meet the entire wish list of the FDA. The concept of public-private partnerships and collaboration highlighted by the FDA, and being contemplated in the food animal industries, present an opportunity for the industry to engage and contribute to the process of national surveillance of ABU.

Assessment of Current Industry Data Sources

Initial efforts have been made to understand the scope and nature of proprietary data on antibiotic use that is held within the industry. This has been done through a combination of personal visits to large 5 production systems, and development and administration of a survey to approximately 20 systems, as well as discussions with Agri Stats. This process is still incomplete, but responses from approximately half of the systems point to considerable commonalities. Important features of current data sources are

- In large systems, ABU data are generally recorded based on delivery of products to specific sites or groups. It is uncommon that actual records of individual treatments are captured electronically although they are recorded on paper on farms.
- Data sources are maintained both for breeding farms and growing pig populations
- Typically, data are recorded for all sow farms and growing sites in large systems, though in some cases not all growing sites are included.
- Typically retrospective data using the same data collection procedures are available for at least 5 years, and up to 15 years. Therefore there is considerable scope for retrospective assessment of usage.
- Most systems analyze antibiotic cost at a flow, farm or site level.
- Most systems can retrieve data on amounts at a drug or product level.
- Feed grade usage in some systems would need to be calculated from feed deliveries
- The units for allocating use tend to be variable among farms and may be at a site, barn or lot level for growing pigs.
- Approximately half of systems are already benchmarking ABU within their operations
- Approximately half of systems record use by route of administration, or at least record use in feed separately from other routes (injection, water)
- Use is not recorded in relation to specific diagnosis in any system to date.
- Approximately half of systems record purpose of treatment with respect to treatment, control and prevention, and less by illness type (e.g., respiratory, enteric, etc.)
- Respondents were generally positive about the potential value to their enterprise and to the industry of being able to benchmark antibiotic use and trends across the industry

- Agri Stats currently benchmarks antibiotic cost for a substantial segment of breeding and growing production. The data collected is purely financial, plus an indication of what products have been used (up to 3 per record), but without quantitative information. The situation with MetaFarms is being pursued.

Recommendations

- Any initiatives to be pursued should be mindful of the attributes listed by the FDA
It is unlikely that any individual projects or data sources will meet all of the objectives listed by the FDA. A number of potential avenues for initial work are listed in the final bullet point
- Formation of a technical committee on antibiotic use surveillance to direct industry leadership on ABU initiatives. This would initially involve selected individuals with interest and expertise in ABU measurement from industry, AASV, academia, and possibly entities involved in industry data analysis (e.g., Agri Stats, MetaFarms)
- Implementation of a pilot activities as a ‘proof of concept’ based on data that are currently collected to define the feasibility, scope and barriers to ABU surveillance based on voluntary sharing of data. It is suggested that relevant activities that all warrant pursuit include:
 - Evaluation of the retrospective industry data that could provide baseline data for a substantial period before implementation of guidelines 209/213.
 - Alignment of current industry data sources with the attributes recently listed by the FDA as necessary in a national surveillance program
 - Given the prevalence of multi-site production and specialized farrow-to-wean farms in the USA, assessment should be made of the relative importance of ABU surveillance in the breeding (approximately 10% of inventory) vs. the growing pig populations (approximately 90% of inventory).
 - Assess the biases inherent in current industry data sources with respect to the national herd for both breeding and growing herds (e.g. in relation to NASS and NAHMS data on industry demographics).
 - Discuss the merit and feasibility of separate (or at least asymmetric) efforts to quantify ABU in breeding and growing populations (analogous to the beef industry)

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